AMENDMENTS TO THE CLAIMS

Please amend claims 87 and 90-98 as follows. No new matter is added by way of these amendments. Consideration and entry of the new claims are respectfully requested.

1-54. (canceled)

55. (previously presented) A transgenic rat whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the regulatable promoter in the absence of a repressor-activator fusion polypeptide-binding compound and does not bind to the regulatable promoter in the presence of the compound, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a chondrocyte-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the rat until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the rat.

56. (previously presented) The transgenic rat of claim 55, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

57. (previously presented) The transgenic rat of claim 56, wherein the matrix metalloproteinase is MMP-13.

58. (canceled)

59. (previously presented) The transgenic rat of claim 57, wherein the MMP-13 comprises the sequence of SEQ ID NO:1 or SEQ ID NO:21.

60. (previously presented) The transgenic rat of claim 55, wherein the repressor-activator fusion polypeptide is a chimeric tetracycline repressor-VP16 transcription activator polypeptide and the regulatable promoter is a Tn10 sequence linked to a portion of the CMV IE promoter.

61. (previously presented) The transgenic rat of claim 60, wherein the regulatable promoter comprises the sequence of SEQ ID NO:2.

62. (previously presented) The transgenic rat of claim 55, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

63. (previously presented) The transgenic rat of claim 55, wherein the chondrocyte-specific promoter is a Type II collagen promoter.

64. (previously presented) A transgenic rat whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a tetracycline-regulatable promoter; and

(b) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the tetracycline regulatable promoter in the absence of tetracycline or a tetracycline analog and does not bind to the regulatable promoter in the presence of tetracycline or tetracycline analog, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a chondrocyte-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the rat until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the rat.

65. (previously presented) The transgenic rat of claim 64, wherein the matrix metalloproteinase is constitutively enzymatically active MMP-13, the tetracycline-regulatable promoter is tet07, the repressor-activator fusion polypeptide is tTA, and the chondrocyte-specific promoter is a Type II collagen promoter.

66. (previously presented) The transgenic rat of claim 64, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

67. (previously presented) A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises:

(a) maintaining the transgenic rat of claim 55 in presence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic rat by withholding the compound from the rat after the rat has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic rat.

68. (previously presented) The method according to claim 67, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

69-71. (canceled)

72. (previously presented) A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises

(a) maintaining the transgenic rat of claim 64 in the presence of tetracycline or a tetracycline analog until adulthood; and

(b) activating expression of the matrix metalloproteinase by withholding the tetracycline or tetracycline analog from the rat after the rat has reached adulthood, such that the matrix metalloproteinase degrades Type II collagen in the joints of the transgenic rat.

73. (previously presented) The method according to claim 72, wherein the tetracycline analog is doxycycline.

74. (previously presented) The method according to claim 72, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

75. (previously presented) A transgenic non-human rat whose genome comprises:

(a) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen, wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(b) a nucleotide sequence encoding a transcription activator protein that binds to the regulatable promoter in the presence of a transcription activator protein-binding compound and does not bind to the regulatable promoter in the absence of the compound, which nucleotide sequence encoding the transcription activator protein is operatively linked to a chondrocyte-specific promoter;

wherein expression of the metalloproteinase is capable of being repressed in the rat until adulthood, and wherein the metalloproteinase is capable of being expressed in the rat during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the rat.

76. (previously presented) The transgenic rat of claim 75, wherein the matrix metalloproteinase is selected from the group consisting of MMP-1, MMP-8, and MMP-13.

77. (previously presented) The transgenic rat of claim 76, wherein the matrix metalloproteinase is MMP-13.

78. (canceled)

79. (previously presented) The transgenic rat of claim 77, wherein the MMP-13 comprises the sequence of SEQ ID NO:1 or SEQ ID NO:21.

80. (previously presented) The transgenic rat of claim 75, wherein the chondrocyte-specific promoter is a Type II collagen promoter.

81. (previously presented) The transgenic rat of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to an ecdysone receptor ligand-binding domain, and wherein the transgenic rat further comprises a nucleotide sequence encoding a retinoid X receptor (RXR), which nucleotide sequence encoding RXR is operatively linked to a chondrocyte-specific promoter.

82. (previously presented) The transgenic rat of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a progesterone receptor ligand-binding domain.

83. (previously presented) The transgenic rat of claim 75, wherein the transcription activator protein is a chimeric polypeptide comprising a transactivator domain linked to a steroid binding domain.

84. (previously presented) The transgenic rat of claim 75, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

85. (previously presented) A method for producing degradation of Type II collagen in the joints of a transgenic non-human rat, which method comprises:

(a) maintaining the transgenic rat of claim 75 in the absence of the transcription activator protein-binding compound until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic rat by administering the compound to the rat after the rat has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the rat.

86. (previously presented) A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises:

(a) maintaining the transgenic rat of claim 81 in the absence of ecdysone, an ecdysone analog, or dexamethasone until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic rat by administering ecdysone, an ecdysone analog, or dexamethasone to the rat after the rat has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the rat.

87. (currently amended) A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises:

(a) maintaining the transgenic rat of claim 82 in the absence of ~~mifeprestone~~ mifepristone (RU 486) until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic rat by administering mifepristone (RU 486) to the rat after the rat has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the rat.

88. (previously presented) The method according to claim 86, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

89. (previously presented) The method according to claim 87, wherein the Type II collagen degradation results in a loss of proteoglycan, cleavage of type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, or combinations thereof.

90. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic rat of claim 55

(b) activating expression of the metalloproteinase at the same age during adulthood of the transgenic rats, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic rat; and

(d) comparing the phenotype of the first transgenic rat to which the composition was administered with the phenotype of the second transgenic rat in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic rat or any increased length of time required for the phenotype to develop in the first transgenic rat that has been administered the composition relative to the phenotype in the second transgenic rat, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

91. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate

morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic rat of claim 60;

(b) activating expression of the metalloproteinase at the same age during adulthood of the transgenic rats, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic rat; and

(d) comparing the phenotype of the first transgenic rat to which the composition was administered with the phenotype of the second transgenic rat in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic rat or any increased length of time required for the phenotype to develop in the first transgenic rat that has been administered the composition relative to the phenotype in the second transgenic rat, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

92. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in

joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic rat of claim 64;

(b) activating expression of the metalloproteinase at the same age during adulthood of the transgenic rats, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic rat; and

(d) comparing the phenotype of the first transgenic rat to which the composition was administered with the phenotype of the second transgenic rat in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic rat or any increased length of time required for the phenotype to develop in the first transgenic rat that has been administered the composition relative to the phenotype in the second transgenic rat, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

93. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which degradation results in a phenotypic change selected from the group consisting of loss

of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic rat of claim 75;

(b) activating expression of the metalloproteinase at the same age during adulthood of the transgenic rats, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic rat; and

(d) comparing the phenotype of the first transgenic rat to which the composition was administered with the phenotype of the second transgenic rat in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic rat or any increased length of time required for the phenotype to develop in the first transgenic rat that has been administered the composition relative to the phenotype in the second transgenic rat, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

94. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat,

which degradation results in a phenotype selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic rat of claim 81;

(b) activating expression of the metalloproteinase at the same age during adulthood of the transgenic rats, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic rat; and

(d) comparing the phenotype of the first transgenic rat to which the composition was administered with the phenotype of the second transgenic rat in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic rat or any increased length of time required for the phenotype to develop in the first transgenic rat that has been administered the composition relative to the phenotype in the second transgenic rat, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

95. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic rat of claim 82;

(b) activating expression of the metalloproteinase at the same age during adulthood of the transgenic rats, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic rat; and

(d) comparing the phenotype of the first transgenic rat to which the composition was administered with the phenotype of the second transgenic rat in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic rat or any increased length of time required for the phenotype to develop in the first transgenic rat that has been administered the composition relative to the phenotype in the second transgenic rat, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

96. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic rat, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic rat of claim 83;

(b) activating expression of the metalloproteinase at the same age during adulthood of the rats, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic rat; and

(d) comparing the phenotype of the first transgenic rat to which the composition was administered with the phenotype of the second transgenic rat in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic rat or any increased length of time required for the phenotype to develop in the first transgenic rat that has been administered the composition

relative to the phenotype in the second transgenic rat, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

97. (currently amended) A method for producing degradation of Type II collagen in the joints of a transgenic rat, which method comprises:

(a) maintaining the transgenic rat of claim 83 in the absence of ~~mifeprestone~~ mifepristone (RU 486) until adulthood; and

(b) activating expression of the matrix metalloproteinase in the transgenic rat by administering mifepristone (RU 486) to the rat after the rat has reached adulthood such that the matrix metalloproteinase degrades Type II collagen in the joints of the rat.

98. (currently amended) A method for evaluating the potential of a composition to counteract degradation of Type II collagen in joints of a transgenic mouse, which degradation results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof, which method comprises:

(a) providing a first and second transgenic mouse, whose genomes each comprise:

([[I]]i) a nucleotide sequence encoding a constitutively enzymatically active human matrix metalloproteinase that cleaves Type II collagen,

wherein the nucleotide sequence encoding the metalloproteinase is operatively linked to a regulatable promoter; and

(ii) a nucleotide sequence encoding a repressor-activator fusion polypeptide that binds to the regulatable promoter in the absence of a repressor-activator fusion polypeptide-binding compound and does not bind to the regulatable promoter in the presence of the compound, which nucleotide sequence encoding the repressor-activator fusion polypeptide is operatively linked to a chondrocyte-specific promoter,

wherein expression of the metalloproteinase is capable of being repressed in the mouse until adulthood, and wherein the metalloproteinase is capable of being expressed in the mouse during adulthood to a level sufficient to cause Type II collagen degradation in the joints of the mouse;

(b) activating expression of the metalloproteinase at the same age during adulthood of the transgenic mice, wherein expression of the metalloproteinase results in a phenotypic change selected from the group consisting of loss of proteoglycan, cleavage of Type II collagen into a TCA degradation product, a change in joint function, joint space narrowing, destruction of cartilage, a change in growth plate morphology, fibrillation and loss of articular cartilage, osteophyte formation, and combinations thereof;

(c) administering the composition to the first transgenic mouse; and

(d) comparing the phenotype of the first transgenic mouse to which the composition was administered with the phenotype of the second transgenic mouse in which the composition was not administered,

wherein any less extensive development in the nature or extent of the phenotype in the first transgenic mouse or any increased length of time required for the

phenotype to develop in the first transgenic mouse that has been administered the composition relative to the mouse phenotype in the second transgenic mouse, indicates the potential of the composition to counteract ~~the phenotypic change~~ degradation of Type II collagen in joints.

99. (previously presented) The method of claim 98, wherein the repressor-activator fusion polypeptide of the transgenic mouse is a chimeric tetracycline repressor-VP16 transcription activator polypeptide and the regulatable promoter is a Tn10 sequence linked to a portion of the CMV IE promoter.

100. (previously presented) The method of claim 98, wherein the regulatable promoter is a tetracycline-regulatable promoter and the repressor-activator fusion polypeptide-binding compound is tetracycline or a tetracycline analog.